# Depression as a Risk for Cancer Morbidity and Mortality in a Nationally Representative Sample

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The relative risks for cancer morbidity and mortality associated with depressive symptoms were examined using data from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. The Center for Epidemiologic Studies Depression scale and the depression subscale from the General Well-being Schedule were used as predictors in this 1 O-year follow-up study of a nationally representative sample. No significant risk for cancer morbidity or mortality was associated with depressive symptoms with or without adjustment for age, sex, marital status, smoking, family history of cancer, hypertension, and serum cholesterol level. These data were also reanalyzed for subjects aged 55 years or older who were retraced by a second follow-up. Neither measure of depressive symptoms was a significant risk for cancer death during the 15-year follow-up interval. These results call into question the causal connection between depressive symptoms and cancer morbidity and mortality.

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THE CONNECTION between emotional distress and disease has received considerable attention during the past several decades.' Although the majority of attention has focused on heart disease and hypertension, other chronic conditions such as allergies, susceptibilities to infection, autoimmune diseases, and cancer have also been investigated.

For editorial comment see p 1231.

Immunologic and hormonal dysfunctions have been identified as the most likely mechanism for linking emotional distress and disease, particularly cancer[2(p180)]:

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There is abundant evidence that emotional factors, particularly failure of psychological defenses, play a role in the onset and course of infectious and neoplastic diseases, resistance to which is immunological, and in the onset and course of allergic and autoimmune diseases, which are associated with immunological abnormalities.

Psychological depression has been identified as one of several emotional conditions that may influence immunologic and hormonal functioning,'.' and depression has been proposed as an important source of vulnerability that leads to morbidity or mortality.[6,7] The association between depression and cancer has been the focus of several studies and reviews.'." The major evidence for the association of depression with cancer mortality was provided by Shekelle and colleagues" and Persky and colleagues." In 17- and ZO-year follow-ups of a random sample of 2020 men employed by the Western Electric Company, in Chicago, Ill, they found a twofold increase in the risk for death from cancer associated with scores on the Minnesota Multiphasic Personality Inventory Depression (MMPI-D) scale. Although not statistically significant, they also found an association between death from noncancerous causes and scores on the MMPI-D scale. These results are particularly notable because depression remained a significant independent predictor of cancer mortality even after statistical adjustment for the influences of age, cigarette smoking, alcohol intake, family history of cancer, and occupational status.

On the other hand, in a large-scale prospective cohort study of 8932 women during a 10- to 14-year follow-up period, Hahn and Petitti[14] failed to find an association between MMPI-D scores and breast cancer in women who were initially free of cancer. Even among women who had severe depression (MMPI-D score ≥70) at the time of entry, no difference was found in the risk for developing breast cancer. Similarly, Weissman et al[15] found that depressive symptoms did not predict subsequent mortality in a 6-year follow-up of 515 subjects who were randomly sampled for a community mental health catchment area study. Even more compelling evidence for the lack of association between depressive symptoms and cancer was provided by Kaplan and Reynolds" in a 17-year follow-up of a representative sample of 6848 subjects who were initially free of cancer. Dattore et al[17] found that men who subsequently developed any type of cancer had significantly lower initial MMPI-D scores. They rejected the notion that depres-

sion is a form of cancer proneness.

In a broader context, neuroticism or emotional distress" is a major dimension of individual differences in personality, of which depressive symptoms are one facet. Several prospective studies have failed to find risk for mortality associated with neuroticism. Keehn et al[19] found no differences in cancer mortality in a 25-year follow-up of 9000 neurotic and matched control subjects. Similar findings were also reported by Coryell et al[20] in a 35-year follow-up study and by Coryell[21] in a 42-year follow-up study. These studies did not find the predicted connection between emotional distress and disease, the ramifications of which were summarized in an editorial by Angell[22(p1572)]:

> There is overwhelming evidence that certain personal habits, such as smoking cigarettes, drinking alcohol, and eating a diet rich in cholesterol and saturated fats, can have great impact on health. However, it is time to acknowledge that our belief in disease as a direct reflection of mental state is largely folklore.

Before one can dismiss the influence of emotional distress on disease, it is important to examine in unselected samples prospectively gathered data based on multiple predictors related to objective health outcomes. It is also important to determine whether specific facets of emotional distress (anxiety, depression) are differentially related to disease outcomes (heart disease, cancer). In the present study, we examine the risks for total cancer morbidity and mortality attributable to symptoms of depression in a lo-year follow-up study of the National Health and Nutrition Examination Survey. The National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study is the first national cohort study of a probability sample of adults in the United, States based on comprehensive medical and dietary examinations.

## PROCEDURES

### Subjects and Measures

Between 1971 and 1975, medical risk factor and psychological data were collected as part of the National Health and Nutrition Examination Survey,[23-25] a stratified probability survey of the adult, noninstitutionalized, civilian population of the United States. Two psychological measures relevant to depressive symptoms were administered: the Cheerful vs Depressed subscale (GWB-D) from the General Well-being Schedule[26,27] was completed by 6913 subjects; and the Center for Epidemiologic Studies Depression (CES-D) scale[28] was completed by 2814 subjects, all of whom had also completed the GWB-D subscale. The sampling design of the National Health and Nutrition Examination Survey ensured that the subjects who took these tests were stratified probability samples of the US population. Consequently, the subjects who took the GWB-D subscale were a representative sample of the United States, as were the subjects who took the CES-D scale.

Beginning in 1981, the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study collected medical outcome data on the original sample." The National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study traced 6410 subjects (93%) of the original GWB-D sample of whom 5579 subjects (87% of those traced) were alive, and 2586 subjects (92%) of the original CES-D sample of whom 2401 subjects (93% of those traced) were alive. The mean follow-up duration was 9.4 years for subjects in the GWB-D sample who were alive at the time of follow-up and 8.2 years for subjects in the CES-D sample who were alive at the time of follow-up (the GWB-D subscale was introduced a year earlier than the CES-D scale). Medical outcome data were coded from death certificates for those subjects who had died since the initial survey, and morbidity information was collected from hospitalization records. Trained coders transformed this information into classifications according to the *International Classification of Diseases, Ninth Revision.*

Beginning in 1986, subjects who were 55 years or older at the time of initial testing were retraced to examine health changes in an elderly cohort. Vital status data were collected from 3814 (96%) of the 3980 eligible subjects who were alive at the time of the first follow-up. Although the second follow-up was limited by subjects' initial ages, and although the follow-up interval was only 4 years, these data provide an opportunity to extend our earlier findings to a high-risk group for a longer interval.

### Psychological Measures

The CES-D scale is a 20-item inventory developed by the National Institute of Mental Health Center for Epidemiologic Studies to assess the frequency and severity with which symptoms of depression were experienced in the past week, The inventory has been extensively validated"',"[29] and is widely accepted in epidemiologic studies of depression in general populations. The CES-D scale is strongly correlated with other self-reported depression inventories and with variables closely related to clinical diagnoses of depression'"; scores for clinically depressed patients are much higher than those for normal subjects,"' and a standard cutoff score of 16 has been defined to assess depressive symptomatology.[32] This score has been demonstrated as identifying a large proportion of individuals with major depressive disorders."' In this sample, the internal consistency of the CES-D scale was 0.85.

The General Well-being Schedule is an 18-item measure of overall subjective well-being, which also contains six subscales that assess freedom from health worry, energy level, satisfying and interesting life, cheerful vs depressed mood (GWB-D subscale), relaxed vs tense or anxious, and emotional behavior control. Each of these subscales has been validated; the GWB-D subscale predicted interviewers' ratings of depression and was highly correlated with other instruments specifically designed for diagnosing clinical depression, including the Zung Depression Scale and the Psychiatric Symptoms Scale." In the present study, the GWB-D subscale, which contains 4 items that measure unhappiness, sadness, discouragement, and lack of cheerfulness, was used as a second measure of depressive symptoms; a cutoff score of 13 was defined to assess depressive symptoms. In this sample, the internal consistency of the GWB-D subscale was 0.78, and the correlation between CES-D and GWB-D scores was .71 ($N = 2814$, $P < .01$).

The CES-D scale and the GWB-D subscale are psychometrically valid measures of depressive symptoms. Although these measures are associated with clinical diagnoses of depression, they are not synonymous with diagnoses themselves, and individuals classified as being depressed by the CES-D scale or the GWB-D subscale might not be considered clinically depressed.

The CES-D scale asks respondents about their feelings during the past week; the GWB-D subscale asks about the past month. It is unlikely that temporary mood states at one point in time would contribute to the development of cancer, so it is essential to establish that both instruments actually assess chronic distress. The CES-D scale and two of the GWB-D items were readministered to all subjects in the follow-up interview. Comparison of initial classification (depressed vs nondepressed) with follow-up classification showed that 83% of the subjects received the same classification on the CES-D scale, and 89% received the same classification on the two-item GWB-D subscale. These data strongly suggest that these instruments provide a relatively stable mea-

Table 1 .-Rates of Cancer Mortality and Cancer Morbidity for Individuals Classified by Depression Status

| Outcome | No./Total No. (%) of Individuals* CES-D Depression | GWB-D Depression | Any Depression |
|---|---|---|---|
| Cancer mortality | | | |
| Not depressed | 42/2100 (2) | 182/5047 (4) | 180/4901 (4) |
| Depressed | 5/347 (1) | 33/746 (4) | 35/892 (4) |
| **Total†** | **47/2447** (2) | **215/5793** (4) | **215/5793** (4) |
| Cancer morbidity | | | |
| Not depressed | 165/2214 (7) | 482/5555 (9) | 471/5399 (9) |
| Depressed | 27/371 (7) | 87/846 (10) | 98/1002 (10) |
| Total | **192/2585** (7) | **569/6401‡** (9) | **569/6401‡** (9) |
| Any cancer | | | |
| Not depressed | 176/2214 (8) | 539/5557 (10) | 527/5401 (10) |
| Depressed | 29/371 (8) | 98/846 (12) | 110/1002 (11) |
| Total | 20512585 (8) | **637/6403** (10) | **637/6403** (10) |

*CES-D indicates Center for Epidemiologic Studies Depression scale; and GWB-D, General Well-being Schedule, Cheerful vs Depressed subscale.
†Excludes subjects who died of causes other than cancer.
‡Two subjects excluded because of missing survival times

sure of depressive symptoms. If chronic depression is related to cancer, these scales should be predictive.

### Analyses

The analyses of depressive symptoms as a risk for cancer morbidity and mortality were performed by the method of proportional hazards.“,” The relative risks (RRs) for morbidity and mortality associated with depressive symptoms were examined in two separate analyses. In the first, the unadjusted risk for cancer morbidity and mortality associated with depressive symptoms alone was calculated. In the second, the adjusted risk was calculated independent of the effects of sex, age at the time of initial testing (age ≥60 years), marital status (married vs unmarried), smoking history (smoked at least 100 cigarettes), family history of cancer, hypertension (systolic pressure >140 mm Hg or diastolic pressure >90 mm Hg), and serum cholesterol level (cholesterol >6.5 mmol/L). Subjects with causes of death other than cancer were excluded from the mortality analyses. Otherwise, all subjects who were traced by the follow-up were included in these analyses, regardless of their health status at the time of initial testing. We also examined the risk for death from cancer associated with both CES-D and GWB-D scores during the 15-year interval between initial testing and the second follow-up.

The influence of the CES-D and GWB-D cutoff points on the results were examined in separate reanalyses of the CES-D scale using 14, 15, 17, and 18 as cutoff scores and GWB-D subscale using 11, 12, 14, and 15 as cutoff scores. Several alternative models were also examined in which body mass index and alcohol consumption were included as predictors. Additional analyses were restricted to men or women separately, or to only white men. To examine the effect of dichotomizing age, all of these analyses were reexamined by substituting age in years for age dichotomized at 60 years. Finally, these analyses were repeated after eliminating subjects with any evidence of cancer based on a physician's examination at the time of the initial interview.

## RESULTS

### Cancer Risk

Table 1 shows the rates of cancer mortality and cancer morbidity for subjects classified by depression status. Deaths caused by cancer were recorded for 47 subjects in the CES-D subsample; within depression groups, deaths from cancer were recorded for 5 (1%) of the 347 depressed subjects and 42 (2%) of the 2100 nondepressed subjects. Cancer diagnoses were recorded for 192 subjects; within depression groups, 27 (7%) of the 3'71 depressed and 165 (7%) of the 2214 nondepressed subjects had cancer diagnoses. As shown in Table 1, similar results were found for the 215 deaths from cancer in the GWB-D subsample; within depression groups, deaths from cancer were recorded for 4% of the depressed and 4% of the nondepressed subjects. No significant bivariate associations were found for cancer morbidity or mortality with either measure of depressive symptoms. Because hospital diagnoses were not recorded before all deaths from cancer, we combined the morbidity and mortality outcomes into a single outcome called “any evidence of cancer.” As shown in Table 1, any evidence of cancer was recorded for 205 subjects in the CES-D subsample (8% of depressed, 8% of nondepressed) and for 637 subjects in the GWB-D subsample (12% of depressed, 10% of nondepressed).

The unadjusted and adjusted RRs for cancer morbidity and mortality associated with CES-D and GWB-D scores are shown in Table 2. The unadjusted RR for cancer mortality associated with CES-D score was nonsignificant (RR = 0.7), indicating the absence of significant differences in survival time associated with depressive symptoms measured by the CES-D scale. Adjusting for the effects of common risk factors (sex, age at the time of initial testing, marital status, smoking history, family history of cancer, hypertension, serum cholesterol level) did not materially change the results, yielding a RR for cancer mortality of 0.6 associated with CES-D score. Significant risks for death from cancer were associated with sex (men more likely than women, RR = 2.1 [confidence interval (CI), 1.0 to 4.4]) and age (older subjects more likely than younger subjects, RR = 4.1 [CI, 2.1 to 8.0]). Similar results were found for CES-D score as a risk for cancer diagnosis (unadjusted RR = 1.0; adjusted RR = 0.9). Significant risks for cancer morbidity were found for sex (men less likely than women, RR = 0.5 ICI, 0.4 to 0.7]) and age (older subjects more likely than younger subjects, RR = 1.8 [CI, 1.3 to 2.5]). Table 2 also shows the RRs for any evidence of cancer associated with CES-D score. Neither the unadjusted (RR = 1.0) nor the adjusted (RR = 0.9) RRs were significant. Significant risks for any evidence of cancer were found for sex (men less likely than women, RR = 0.6 [CI, 0.4 to 0.8]) and age (older subjects more likely than younger subjects, RR = 2.0 [CI, 1.5 to 2.81).

The GWB-D score was neither a significant unadjusted (RR = 1.2) nor a significant adjusted (RR = 1.3) risk for cancer mortality. In this subsample, significant risks for cancer mortality were found for sex (men more likely than women, RR = 2.0 [CI, 1.4 to 2.8]), age (older subjects more likely than younger subjects, RR = 5.4 [CI, 3.9 to 7.5]), and cigarette smoking (smokers more likely than nonsmokers, RR = 1.5 [CI, 1.1 to 2.1]). Similarly, GWB-D score was not a significant risk for cancer diagnosis (unadjusted RR = 1.2; adjusted RR = 1.2). Significant risks for cancer diagnosis were found for sex (women more likely than men, RR = 0.7 [CI, 0.6 to 0.8]), age (older subjects more likely than younger subjects, RR = 2.0 [CI, 1.7 to 2.4]), family history of cancer (subjects with a family history more likely than those without such a history, RR = 1.3 [CI, 1.1 to 1.6]), and marital status (married subjects more likelythanunmarried, RR = 1.3 [CI, 1.0 to 1.6]). The risk for cancer mortality

Table 2.—Unadjusted and Adjusted Relative Risks (RRs) and 95% Confidence Intervals (CIs) for Cancer Morbidity and Mortality by CES-D Rating and GWB-D Rating*

| | CES-D Depression | | GWB-D Depression | | Any Depression | |
|---|---|---|---|---|---|---|
| Outcome | RR | CI | RR | CI | RR | CI |
| Cancer mortality | | | | | | |
| Unadjusted | 0.7 | 0.3-1.8 | 1.2 | 0.9-1.8 | 1.1 | 0.8-1.6 |
| Adjusted | 0.6 | 0 2-1.9 | 1.3 | 0.8-2.0 | 1.2 | 0.8-1.8 |
| Cancer morbidity | | | | | | |
| Unadjusted | 10 | 0.7-1.5 | 1.2 | 1.0-1.5 | 1.1 | 0.9-1.4 |
| Adjusted | 0.9 | 0.6-1.3 | 1.2 | 0.9-1.5 | 1.1 | 0.9-1.4 |
| Any cancer | | | | | | |
| Unadjusted | 10 | 0.7-1.5 | 1.2 | 1.0-1.5 | 1.2 | 0.9-1.4 |
| Adjusted | 0.9 | 0.6-1.4 | 1.2 | 0.9-15 | 1 1 | 0 9-1 4 |

*Adjusted for sex, age, marital status, smoking habit, family history of cancer, hypertension, and cholesterol level. All RRs nonsignificant (all $P > .05$). Number of subjects shown in Table 1 for unadjusted analyses; numbers of subjects for adjusted analyses are smaller (2212 to 5729) because of missing data on other variables. CES-D indicates Center for Epidemiologic Studies Depression scale; and GWB-D, General Well-being Schedule, Cheerful vs Depressed subscale

was significantly greater for men, but the risk for cancer morbidity was significantly greater for women. These apparently contradictory findings suggest that men have shorter survival times, which are probably related to the prevalence of lung cancer among men, particularly in view of the significant risk for mortality associated with cigarette smoking. Moreover, these results also suggest that cancer diagnoses occur earlier for women, probably because of the emphasis on early detection of breast and uterine cancers.

The GWB-D score was neither a significant unadjusted (RR = 1.2) nor adjusted (RR = 1.2) risk for any evidence of cancer. Significant risks for any evidence of cancer were found for sex (women more likely than men, RR = 0.8 [CI, 0.6 to 0.9]), age (older subjects more likely than younger subjects, RR = 2.1 [CI, 1.8 to 2.6]), and family history of cancer (subjects with a family history more likely than those without such a history, RR= 1.3 [CI, 1.1 to 1.51). In addition to examining the separate risks for cancer associated with CES-D and GWB-D scores, we also examined the risk associated with any evidence of depression, where depressive symptoms were defined as exceeding the cutoff point on either the CES-D scale or the GWB-D subscale. As shown in Table 2, any evidence of depressive symptoms was neither a significant unadjusted nor a significant adjusted risk for cancer mortality, cancer morbidity, or any evidence of cancer.

These results were unrelated to the CES-D and GWB-D cutoff points used to define depression. Neither the CES-D scale nor the GWB-D subscale yielded significant adjusted RRs for death or morbidity from cancer in separate analyses that used 14, 15, 17, and 18 as the CES-D cutoff score and 11, 12, 14, and 15 as the GWB-D cutoff score. No significant RRs were found when analyses were restricted to men or women or to white men. Adding the influences of body mass index and frequency of alcohol consumption did not change these results: neither were significant predictors of the outcome measures. Also, the substitution of age in years for age dichotomized at 60 years did not change the results. Finally, these results were unchanged after eliminating subjects with any evidence of cancer based on a physician's examination at the time of the initial survey.

### SubsequentFollow-ups

Beginning in 1986, subjects who were 55 years or older at the time of initial testing were retraced to examine health changes in an elderly cohort. In this second follow-up, vital status data were collected from 3814 (96%) of the 3980 subjects who were 55 years or older at the time of initial testing and who were alive at the time of first follow-up. Deaths from cancer were recorded for 63 of 663 subjects in the CES-D subsample and for 224 of 1812 subjects in the GWB-D subsample. Within depression groups defined by the CES-D scale, deaths from cancer were recorded for 6 (7%) of 86 depressed subjects and 57 (10%) of 577 nondepressed subjects. Within depression groups defined by GWB-D scores, deaths from cancer were recorded for 31 (13%) of 236 depressed subjects and 193 (12%) of 1576 nondepressed subjects. There were no significant bivariate associations between death from cancer and depressive symptoms for either the CES-D or GWB-D scores. Similarly, neither the unadjusted (CES-D, RR = 0.7; and GWB-D, RR = 1.1) nor the adjusted (CES-D, RR = 0.7; and GWB-D, RR = 1.2) RRs for death from cancer associated with either the CES-D or GWB-D scores were significant; nor was the risk for death from cancer associated with any depression (unadjusted RR = 1.1 and adjusted RR = 1.2). These results replicated our earlier findings based on the interval between initial testing and the first follow-up.

## COMMENT

The absence of significant differences in cancer mortality or cancer morbidity associated with our two predictors calls into serious question the hypothesis that depressive symptoms are a risk for cancer mortality or morbidity. Our results are strengthened by the use of two well-validated measures in a nationally representative sample and additionally strengthened by two separate replications in a second wave of sampling. Moreover, our results do not depend on a medically selected sample because we performed no prior selection for health status at the time of initial testing.

Although the CES-D scale assesses many aspects of depression that are important for its diagnosis, it was not intended as a substitute for clinical diagnosis. The results of the present study apply only to symptoms of depression and do not address the risks for cancer morbidity and mortality associated with clinical depression. However, Bieliauskas and Garron[9] noted that diagnoses of clinical depression were unrelated to the prospective development of cancer.

Shekelle and colleague? and Persky and colleagues" showed a prospective link between depression and cancer mortality. They studied only middle-aged men, aged 40 to 55 years, whereas the present study examined men and women between the ages of 25 and 75 years. It is possible that the risk for death from cancer caused by depressive symptoms may be sex or race specific. However, our results were unchanged when the present data were reanalyzed separately for men and women and for men initially older than 40 years. Bieliauskas[10] suggested that Shekelle's findings were better interpreted as the effects of "chronic distress" rather than implicating depression per se. However, this reinterpretation of the MMPI-D scale presents a major conceptual problem in that there is an absence of supporting evidence that chronic distress or neuroticism is a risk for mortality.[18] Neuroticism, which encompasses all of the various forms of chronic psychological distress (eg, anxiety, anger, depression), is not a risk for mortality, although it is strongly related to health-care seeking, somatic complaints, and illness behaviors.

There are several limitations to this study. As in any prospective study, it was not possible to trace all subjects,

and in both CES-D and GWB-D samples subjects whose scores exceeded the cutoff point for depression were less likely to be traced than were nondepressed subjects. It is thus possible that the present lack of association between depressive symptoms and cancer might be accounted for by our inability to trace subjects who were depressed and developed cancer. However, the 93% retracing rate for the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study is excellent by epidemiologic standards, making this interpretation implausible. It is also possible that cancer morbidity was not detected by inpatient records. A longer follow-up interval might have shown an association, but there was no evidence of this in our analyses of the second follow-up. Similarly, a larger sample would increase the statistical power of our analyses to detect an effect. However, the present sample sizes are sufficiently large to detect even a small effect between depressive symptoms and cancer. It would have been useful to have measurements of depression at several points during the interval to assess the chronicity of depression, but analyses from the follow-up showed that both the CES-D and GWB-D scores were strongly related to future depression status. Finally, clinical diagnoses or alternative measures of depression might have predicted the development of cancer, but neither of the two scales used in the present study showed such an association. Although no study is definitive, the weight of evidence casts considerable doubt on a connection between depressive symptoms and cancer morbidity and mortality.

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